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TITLE: Targeting Prostate Cancer Cells by Combined Oxidative Stress Induction and Androgen Receptor Antagonism

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14. ABSTRACT
Efficient synthetic routes were developed for the synthesis of Enzalutamide (Enz, MDV-3100) and EPI-001 derived hybrid drugs that target AR C-terminal ligand binding domain or N-terminal domain meanwhile inducing oxidative stress. Five classes of hybrid drugs have been designed and synthesized, i.e. Enz-PL (e.g. compd **28**), Enz-catechol (e.g., compds **29**, **30**), Enz-HDACi (e.g., compds **24**, **31**, **33**), chirally pure EPI scaffold carrying alternative electrophiles (i.e. compds **53**, **55**, **58** and **60**). Biological assays, e.g., anti-proliferation assay, AR luciferase reporter assay and visualization of AR distribution in human prostate stromal cells were successfully established in collaborator's lab and will be used to study novel multifunctional hybrid drugs. Effects of Enz and piperlongumine (PL) on LAPC4 cell proliferation were also investigated, both compounds inhibited R1881-induced cell proliferation at 10 μM but not at 1 μM in single drug treatment. After 72h treatment, Enz (10 μM) and PL (10 μM) combination significantly inhibited LAPC4 cell growth compared to Enz treatment alone, the inhibitory effect was also stronger than PL single treatment, but was not statistically significant. Further experiments using combinations with different doses will be conducted. It would be straightforward to expand hybrid drug/drug combination libraries and to conduct structure-activity relationship studies based on current accomplishments.

15. SUBJECT TERMS
Key Words: oxidative stress, AR antagonist, anti-androgens, hybrid drug, drug combinations

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Grant had been temporally unavailable since PI left UIC on September 12, 2013 and joined Wayne State University as an Assistant Professor. The award was waiting for the pending transfer to be completed. No research had been performed during this period of time.

Grant transfer was completed on July 22, 2015. Research have been resumed and we are successfully making progress at this moment. New results will be reported next year (due on Aug 21, 2016). The support from DoD is highly appreciated!